D1

glycine (CSVTCG) (SEQ ID NO. 14), the same type I repeat shown to have anti-angiogenic activity. (14, 15).

On Page 9, please amend the last paragraph beginning with "Figure 1" to read as follows:

Figure 1. HRGP contains CLESH-1 homology (thrombospondin-binding) motifs. Amino acid sequence alignment of CD36/LIMPII TSP binding motifs with homologous sequences in HRGP. Results of pattern-based search (BEAUTY) using CD36 exon 5 coding region (CD36 aa 95-143) within SEQ ID NO: 18 as query identified a split CLESH-1 motif in HRGP (SEQ ID NO.1: aa 443-517). Optimization of alignments using SIM, ALIGN, and LALIGN programs also identified additional repeating motifs (SEQ ID NO.2: shown, aa 173-230). Amino acids identical between HRGP and either CD36 or LIMPII are highlighted white on black. Bold residues and pattern symbols represent conservative substitutions according to the following groups: basic [KRH, (+)]; acidic [DE, (-)]; charged [KRH, DE, ($)]; aromatic [YFW,(@)]; aliphatic [AG, (a)]; short chain [GA, STP, (!)]; hydrophobic [AGP, IVL, FM, (Δ)]; polar/hydrophilic [ST, KRH, DNEQ, CWY, (±)], hydroxyl [STY], and nonpolar/branched [IVL]. GenBank™/EMBL accession numbers: huHRGP, P04196; huCD36, M24795; huLIMPII, D12676.

D2

On Page 10, please amend the last paragraph beginning with "The thrombospondin-binding" to read as follows:

The thrombospondin-binding motifs are disclosed as amino acid sequences 443-517 (SEQ ID NO. 1) and 173-230 (SEQ ID NO. 2) of HRGP as shown in Figure 1. The full amino acid sequence (1-525) of human HRGP is provided in GenBank under accession number P04196.

D3

On Page 12, please amend the first paragraph beginning with "The thrombospondin-binding" to read as follows:

The thrombospondin-binding motifs of the present invention also include functional fragments and homologs of the amino acid sequences 443-517 (SEQ ID NO. 1) and 173-230

D4

(SEQ ID NO. 2) of HRGP (see Figure 1) that retain the ability to bind TSP-1. The functional fragments may include combinations of sequences taken from the amino acid sequence 443-517 (SEQ ID NO. 1) and from the amino acid sequence 173-230 (SEQ ID NO. 2) of HRGP. Homologs of the amino acid sequences 443-517 (SEQ ID NO. 1) and 173-230 (SEQ ID NO. 2) of HRGP include sequence variants of each of these sequences, fragments of these variants and combinations of the fragments of these variants.

On Page 13, please amend the last paragraph beginning with "Functional fragments" to read as follows:

Functional fragments of thrombospondin-binding motifs are defined as those portions of the amino acid sequences shown in Fig. 1 which retain thrombospondin binding activity. Such thrombospondin-binding fragments include, for example, regions 443-517 (SEQ ID NO. 1) and 173-230 (SEQ ID NO. 2); also smaller fragments such as 443-451 (SEQ ID NO. 3); 452-480 (SEQ ID NO. 4); 489-517 (SEQ ID NO. 5); and also 173-179 (SEQ ID NO. 6); 180-200 (SEQ ID NO. 7); and 201-230 (SEQ ID NO. 8).

On Page 14, please amend the first full paragraph beginning with "The thrombospondin-binding sites" to read as follows:

The thrombospondin-binding sites may be comprised of any combination of the above-named fragments. The number of fragments may be any number from 2-10, for example

443-480 (SEQ ID NO. 9) plus 452-480 (SEQ ID NO. 4);

452-480 (SEQ ID NO. 4) plus 489-517 (SEQ ID NO. 5);

443-451 (SEQ ID NO. 3) plus 489-517 (SEQ ID NO. 5);

also other fragments, for example 173-200 (SEQ ID NO. 10); and 180-230 (SEQ ID NO. 11); may be used in combinations of sequences from the two regions, i.e. 443-517 (SEQ ID NO. 1) and 173-230 (SEQ ID NO. 12) such as:

443-480 (SEQ ID NO. 13) plus 180-230 (SEQ ID NO. 11);

D6

443-480 (SEQ ID NO. 9) plus 201-230 (SEQ ID NO. 8); and

180-230 (SEQ ID NO. 11) plus 452-480 (SEQ ID NO. 4) and so on.

On Page 29, please amend the last paragraph beginning with "Optionally, the" to read as follows:

Optionally, the DNA that encodes the fusion protein is engineered so that the fusion protein contains a cleavable site between the protein and the fusion partner. Both chemical and enzymatic cleavable sites are known in the art. Suitable examples of sites that are cleavable enzymatically include sites that are specifically recognized and cleaved by collagenase (Keil et al., FEBS Letters 56:292-296 (1975)); enterokinase (Hopp et al., Biotechnology 6, 1204-1210 (1988) Prickett, K. S. et al., Biotechniques 7:580-589 (1989); LaVallie et al., J. Biol. Chem. 268:23311-23317 (1993)); factor Xa (Nagai et al., Methods Enzymol. 153:461-481 (1987)); and thrombin (Eaton et al., Biochemistry 25:505 (1986) and Chang, J. Y. Eur. J. Biocehem. 151:217-224 (1985)). Collagenase cleaves between proline and X in the sequence Pro-X-Gly-Pro wherein X is a neutral amino acid. Enterokinase cleaves after lysine in the sequence Asp-Asp-Asp-Asp-Lys (SEQ ID NO. 15). Factor Xa cleaves after arginine in the sequence Ile-Glu or Asp-Gly-Arg. Thrombin cleaves between arginine and glycine in the sequence Arg-Gly-Ser-Pro (SEQ ID NO: 19).

D7

On Page 41, please amend the last paragraph beginning with "Reagents:" to read as follows:

Reagents: Recombinant human basic fibroblast growth factor (bFGF) was purchased from R & D Systems Inc. (Minneapolis, MN, USA) or from Research Diagnostics, Inc.(Flanders, NJ, USA). Rabbit antibody to HRGP was kindly supplied by Dr. Lawrence Leung, Stanford University, Palo Alto, CA. Murine monoclonal antibody to TSP-1 (11.4) has been previously described (16). Murine monoclonal antibody to CD36 (FA6) was obtained from the Vth International Workshop on Human Leukocyte Antigens (17). TSP-1 was purified from human platelet releasate by heparin affinity and anion exchange chromatography on Mono Q-Sepharose (Pharmacia Biotech Inc., Piscataway, NJ, USA) as described (3, 16). Radiolabeling was performed with $Na^{125}I$ (Amersham Life Science Inc.,

D8

Arlington Heights, IL, USA) using immobilized chloramine T (IODO-BEADS, Pierce, Rockford, IL, USA) as described (18). Glutathione-S-transferase-CD36 fusion proteins (FP) have been previously described (19). HRGP was purified from human plasma by lys-plasminogen affinity chromatography as described (6). Purified proteins were incubated with polymyxin B-coated agarose (Sigma Chemical Co., St. Louis, MO, USA) to remove any potentially contaminating lipopolysaccharides (LPS) prior to use in cellular assays. Specific rabbit antibody to CSVTCG (SEQ ID NO. 14) was generated by subcutaneous immunization with KLH-coupled peptide. IgG was purified from serum by Protein A chromatography (Pierce).

D8

On Page 44, please amend the first paragraph beginning with "*In vivo* subcutaneous" to read as follows:

In vivo subcutaneous Matrigel plug assays were performed as described (23). Briefly, 500 µl of Matrigel mixed with proteins or growth factors was injected subcutaneously near the abdominal midline of C57B1/6 mice. Gels were removed after 10 days, fixed in 1% paraformaldehyde, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Immunohistochemistry was performed on unstained sections using an anti-human von Willebrand factor (vWF) IgG (Dako, Glostrup, Denmark) or isotype-matched control (Sigma) and a biotin-streptavidin-peroxidase antibody and development system (Vector Laboratories, Burlingame, CA) as described (24) and counterstained with Mayer's hematoxylin (ImmunoGenex, San Ramon, CA, USA). After scanning, the degree of angiogenesis was determined by counts of vWF-positive blood vessels using Scion Image. For breast tissue, frozen sections of freshly obtained human breast carcinoma were incubated with rabbit antibody to HRGP or CSVTCG (SEQ ID NO. 14) or murine monoclonal antibody to TSP, or isotype-matched controls (Sigma), and developed as above. These studies were approved by the Institutional Animal Use Committee.

D9

On Page 45, please amend the second paragraph beginning with "The binding of HRGP" to read as follows:

The binding of HRGP to TSP-1 was inhibited in the presence of 50 µM of the type-1 repeat synthetic peptide CSVTCG (SEQ ID NO. 14), but not by a scrambled peptide,

D10

D10

TVSGCC (SEQ ID NO. 16) or by an RGDS (SEQ ID NO. 17) peptide. However, the binding of plasminogen to TSP-1 was not inhibited by the synthetic peptides. Ligand blots show binding of radiolabelled HRGP to TSP-1 that had been subjected to SDS-PAGE and transferred to nitrocellulose, then developed by autoradiography.

On Page 45, please amend the third paragraph beginning with "The type 1 repeat" to read as follows:

D11

The type 1 repeat of TSP-1 mediates binding to HRGP. HRGP binds to TSP-1 saturably, reversibly, and with high affinity (7nM) (6). Binding of HRGP to immobilized TSP-1 was inhibited by the TSP-1 hexapeptide CSVTCG (SEQ ID NO. 14), whereas the control TSP-1 peptide (RGDS) (SEQ ID NO. 17) and the scrambled peptide (TVSGCC) (SEQ ID NO. 16) had no effect. As an additional control, the binding of plasminogen to TSP-1 was measured. Plasminogen binding was not inhibited by the CSVTCG (SEQ ID NO. 14) peptide (1B), further indicating that this interaction was not mediated by the type I repeats.

On Page 45, please amend the fourth paragraph beginning with "The TSP type 1 repeat" to read as follows:

D12

The TSP type 1 repeat inhibits the binding of HRGP to TSP-1 in a concentration-dependent manner. Varying amounts of HRGP were added alone or in the presence of increasing concentrations of the peptide CSVTCG (SEQ ID NO. 14) to TSP-1 coated wells. Binding was measured by ELISA as described above. Inhibition of TSP-1 binding of HRGP by hexapeptide was concentration-dependent and reached maximum at 50 μM.

On Page 46, please amend the first paragraph beginning with "That the TSP-1-HRGP" to read as follows:

D13

That the TSP-1-HRGP interaction is mediated by the TSP type I repeats is demonstrated by the following: Binding of radiolabelled HRGP to TSP-1 which had been resolved on SDS-PAGE and transferred to nitrocellulose was significantly decreased in the presence of anti-CSVTCG (SEQ ID NO. 14) antiserum and completely abolished by the CSVTCG (SEQ ID NO. 14) peptide (50μM). Inhibition by the TSP-1 type I repeat was concentration dependent and reached maximum at 50 μM.

On Page 46, please amend the third paragraph beginning with "TSP-1 and HRGP c0-localize in stroma of human" to read as follows:

D14

TSP-1 and HRGP co-localize in stroma of human breast carcinoma. Frozen sections of freshly obtained tumor were incubated with monoclonal antibody to TSP-1, polyclonal anti-HRGP, or antiserum to CSVTCG (SEQ ID NO. 14). Slides were developed with a peroxidase-conjugated avidin-biotin second antibody system and examined at 500X magnification. Panels taken from adjacent sections and showed stromal connective tissue bands staining with anti-TSP and anti-HRGP but not anti-CSVTCG (SEQ ID NO. 14). Tumor cell stained with anti-TSP and anti-CSVTCG (SEQ ID NO. 14) but not with anti-HRGP.

On Page 47, please amend the first paragraph beginning with "In order to explore" to read as follows:

D15

In order to explore whether the TSP type 1 repeat is involved in TSP-1-HRGP interactions in the breast cancer stroma, we developed a specific antibody to the CSVTCG (SEQ ID NO. 14) peptide. The antiserum was reactive to plasmodium falciparum circumsporozoite protein, known to contain the peptide, and to purified TSP-1, by Western blot. The CSVTCG (SEQ ID NO. 14) epitope was detectable intracellularly in the breast cancer cells where TSP-1 was detectable but HRGP was absent. However, in the tumor stroma where HRGP co-localized with TSP-1, there was no detectable CSVTCG (SEQ ID NO. 14) reactivity. This provides evidence that TSP-1 associates with HRGP *in vivo*, and that this interaction masks the type I epitope of TSP-1.

On Page 47, please amend the second paragraph beginning with "HRGP contains CLESH-1" to read as follows:

D16

HRGP contains CLESH-1 homology motifs. The binding site for TSP-1 on CD36 and other proteins is defined by homologous, evolutionarily conserved amino acid motifs known as CLESH-1 (18, 28, 29). As shown in figure 1, by sequence alignments of deduced amino acid sequences of HRGP we identified a region (aa 443-517) (SEQ ID NO. 1) with significant homology to the CLESH-1 domain of CD36 and the CD36-related protein